STUDIES ON THE DIETHYLAMIDE OF LYSERGIC ACID. (110)
III. EFFECT OF PHENOXYBENZAMINE ON LSD-REACTION IN MAN.

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A-391

STUDIES ON THE DIETHYLAMIDE OF LYSERGIC ACID.
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A number of the signs and symptoms observed after administration of LSD -- pupillary dilatation, elevation of blood pressure, gooseflesh, anxiety, sense of gastrointestinal oppression, etc. -- suggest hyperactivity of the sympathetic (adrenergic) nervous system. Rothlin and coworkers (1) have postulated that LSD has central vegetative (autonomic) effects. Chlorpromazine partially ameliorates the LSD reaction (2,3,4), and since chlorpromazine is a peripheral (5) and possibly a central (6) adrenergic blocker, one might hypothesize that chlorpromazine ameliorates the LSD reaction by virtue of central adrenergic blocking effects.

Recently Elder *et al.* (7) and Gogerty *et al.* (8) have presented some interesting findings in experimental animals. Pretreatment with chlorpromazine reduces LSD-induced hyperthermia in rabbits and "feline-mania" in cats. If LSD is given to rabbits within two hours after reserpine, hyperthermia is accentuated. At this particular time, release of norepinephrine (9) and serotonin (10) from brain is occurring. If LSD is given

ten hours after reserpine (when norepinephrine and serotonin have been depleted) LSD effects are attenuated. Most important, phenoxybenzamine (dibenzyline), an adrenergic blocker with no known central effects, attenuated "feline-mania" induced by LSD.

Since very large doses of LSD are required to induce definite behavioral changes in animals, and since the relationship of any behavioral change induced in animals to psychotic symptoms in humans is always doubtful, it seemed important to study the effect of phenoxybenzamine on the LSD psychosis in man. The purpose of the present report is to present data showing that pretreatment with phenoxybenzamine did not alter significantly the mental symptoms produced by LSD in human subjects, despite definite evidence of peripheral adrenergic blockade.

GENERAL METHODS

Subjects. All were former morphine addicts serving sentences for violation of narcotic laws who volunteered for the experiments. All were physically healthy adult Negro males who presented no evidence of psychosis on psychiatric examination.

Drugs. LSD tartrate and LSD placebo were administered orally in solution to patients in the fasting state. Phenoxybenzamine and phenoxybenzamine placebo were given in capsules. L-Epinephrine HCL and epinephrine placebo were administered subcutaneously. Specific details on dosage are given under the particular experiments.

Experiments were "double-blind" -- neither the patients nor the observers knew what drugs had been given. In evaluating the effect of phenoxybenzamine on the LSD reaction the following combinations of drugs were administered at intervals of seven days in random balanced order: LSD placebo plus phenoxybenzamine placebo, LSD plus phenoxybenzamine placebo, LSD plus phenoxybenzamine, and LSD placebo plus phenoxybenzamine.

Methods of Measurement. Intensity of the LSD reaction was assessed by methods previously described (11). The following observations were obtained at hourly intervals twice before and eight times after administration of LSD, or LSD placebo: pupillary size, threshold for kneejerk, systolic blood pressure, number of positive answers on a modification of the questionnaire devised by Abramson et al. (12), and the clinical grade, based on a short mental status examination (11). Areas under time-action curves were calculated by the method of Winter and Flataker (13) and results expressed as mm. hours (pupils),

mm. hours (blood pressure), and degree-hours (kneejerk). In addition, resting pulse rates, resting systolic blood pressures, and pulse rates and systolic pressure after standing for one minute were determined and time-action areas calculated. These latter measurements could not always be obtained (experiment 4) due to postural hypotension with resultant fainting on standing.

Effects of epinephrine were assessed by measuring pulse rate and systolic and diastolic blood pressure at the following intervals: 10 minutes before, and immediately before subcutaneous injection of epinephrine or epinephrine placebo; 5, 10, 15, 20, 30, 40, and 60 minutes after injection of epinephrine or placebo. Time-action areas were also calculated for these measurements.

Experiment 1. Effect of 1 mg./kg. of Phenoxybenzamine Reaction Induced by 0.5-1.0 mcgm./kg. of LSD. Phenoxybenzamine or phenoxybenzamine placebo was administered orally in capsules at 6 a.m., and LSD or LSD placebo orally in solution at 8 a.m., thus allowing three to four hours for adrenergic blockade to develop prior to expected peak of LSD effects. Four patients received combinations of 1.0 mcgm. of phenoxybenzamine or phenoxybenzamine placebo with 0.5 mcgm./kg. of LSD or LSD placebo. Since the number of subjects was small, and since the results were similar to the group that received 1.0 mcgm./kg. of LSD, the results will not be presented in detail.

Six patients received combinations of 1.0 mg./kg. of phenoxybenzamine or phenoxybenzamine placebo with 1.0 mcgm./kg. of LSD or LSD placebo. Results are presented in table 1. Both the number of answers and the clinical grade were less after the combination of LSD plus phenoxybenzamine, as compared with LSD alone. The differences, however, were not statistically significant. Phenoxybenzamine did reduce pupillary dilatation significantly after LSD, but had no effect on the LSD-induced rise in resting systolic blood pressure or on the decreased threshold for the kneejerk. Miosis, postural hypotension, and postural tachycardia indicated that some degree of peripheral adrenergic blockade had occurred after phenoxybenzamine alone. LSD was an effective antidote for the postural hypotension after this dose of phenoxybenzamine.

Experiment 2. Blocking of Epinephrine by 1.0 mg./kg. of Phenoxybenzamine. Since no definite attenuation of the LSD reaction was observed in the previous experiment, it seemed wise to determine whether the dose of phenoxybenzamine used would significantly alter the response to epinephrine. Four patients were "challenged" with 0.4 to 0.6 mg./70 kg. of epinephrine subcutaneously before and three hours after ingestion of 1.0 mg./kg. of phenoxybenzamine. Results were controlled by placebo injections before and after phenoxybenzamine. Measurements were those described above under general methods.

Results are shown in table 2. As expected, no blocking of the increase in pulse rate induced by epinephrine was observed after phenoxybenzamine. Rise in systolic blood pressure after epinephrine was reduced by phenoxybenzamine, but the reduction was not significant statistically in this small group. The decrease in diastolic pressure after epinephrine was enhanced after phenoxybenzamine. These results indicated that some degree of adrenergic blockade was present.

Experiment 3. Blocking of Epinephrine by 2.5 mg./kg. of Phenoxybenzamine. Eight patients received 0.5, 1.0 and 1.0 mg./kg. (total of 2.5 mg./kg.) of phenoxybenzamine at 26, 13, and 3 hours prior to challenge with 0.6 mg./70 kg. of epinephrine. A second test with epinephrine was carried out five hours after the last dose of phenoxybenzamine. The results are shown in table 3. A definite diminution in the rise in systolic pressure after epinephrine was observed five hours after the last dose of phenoxybenzamine as well as a marked enhancement of the decline in diastolic blood pressure after both test doses of epinephrine. In addition, all patients were unable to stand quietly for more than a minute without becoming dizzy or fainting. Since these findings were compatible with a considerable degree of adrenergic blockade, this dosage of dibenzyline was used in experiment 4.

Experiment 4. Effect of 2.5 mg./kg. of Phenoxybenzamine (Divided Doses) on the LSD-Reaction. Ten patients received 0.5, 1.0 and 1.0 mg./kg. of phenoxybenzamine (or phenoxybenzamine placebo) 24, 11, and 2 hours prior to 1.0 mcgm./kg. of LSD.

Results are shown in table 4. Although the effects of phenoxybenzamine were so pronounced that 5 of the patients fainted on standing for less than one minute, there was no reduction in the number of symptoms reported or in the intensity (clinical grade) of the reaction after phenoxybenzamine combined with LSD. A significant reduction in pupillary diameter was noted but the other indicators of LSD effect, including the rise in systolic blood pressure, were unaffected. LSD tended to antagonize the effect of phenoxybenzamine on the pulse rate when standing.

DISCUSSION

No definite evidence of attenuation of the LSD-induced mental symptoms by phenoxybenzamine was observed in the experiments described above. It hardly seems likely that this could be due to inadequate dosage of phenoxybenzamine, since signs of a considerable degree of adrenergic blockade were present after phenoxybenzamine (miosis, partial attenuation of

the epinephrine-induced rise in systolic blood pressure, accentuation of epinephrine-induced drop in diastolic pressure, and marked postural hypotension and tachycardia). Even though the adrenergic blockade may not have been complete, the doses of LSD used were small, so some evidence of attenuation of the mental symptoms should have been detected.

Failure of phenoxybenzamine to block the mental changes caused by LSD might indicate that the LSD reaction is not mediated adrenergically, or that phenoxybenzamine lacks central adrenergic blocking actions. Since role of epinephrine and/or norepinephrine as central synaptic transmitters is still speculative, these alternatives cannot be assessed at the present time.

Failure to confirm amelioration of the LSD-reaction observed in animals after phenoxybenzamine emphasizes that care is necessary in extrapolating behavioral changes in animals to mental symptoms in man.

SUMMARY

1.0 mg./kg. of phenoxybenzamine or 2.5 mg./kg. of phenoxybenzamine (divided in three doses) did not attenuate significantly mental changes induced by 0.5 to 1.0 mcgm./kg. of LSD-25.

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A-382

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A-381

A-380

TABLE I.
Effect of 1.0 Mg./Kg. of Phenoxybenzamine on the Reaction Induced by 1.0 Mcgm./Kg. of LSD

MEASURE	TREATMENT			
	LSD Placebo Plus Phenoxybenzamine Placebo	LSD Plus Phenoxybenzamine Placebo	LSD Plus Phenoxybenzamine	LSD Placebo Plus Phenoxybenzamine
Pulse Rate, Recumbent	+ 31.6 ± 16.6	+ 57 ± 14.9	+ 80.3 ± 14.1	38 ± 9.9
Pulse Rate, Standing	+ 45.7 ± 58.3	+ 39 ± 102	+ 82.1 ± 15.1	+ 115 ± 39.3
Systolic Pressure, Recumbent	+ 29.4 ± 11.7	+ 78 ± 5.0	+ 100 ± 18.5	+ 52 ± 15.2
Systolic Pressure, Standing	+ 23.6 ± 10.2	+ 65 ± 17.8	+ 68.9 ± 32.8	- 53 ± 18.3
Pupillary Size	+ 3.7 ± 0.8	+ 12.9 ± 0.7	+ 8.1 ± 1.8	- 1.2 ± 4.2
Pillar Reflex	- 2.8 ± 0.9	+ 5.9 ± 2.0	+ 3.9 ± 1.9	0.44 ± 0.6
Number of Answers	0.33 ± 1.8	49 ± 23	19.4 ± 6.6	0 ± 0
Clinical Grade	0 ± 0	2.2 ± 0.5	1.6 ± 0.6	0 ± 0

Figures are means ± standard errors of observations on 6 patients. In case of pulse rate, blood pressure, pupillary diameter, and patellar reflex, they represent time-action calculations (areas) and are expressed as beat-hours (pulse rate), mm. hours (blood pressure), etc. Number of answers represents number of positive responses on questionnaire after LSD (or LSD placebo) which were not scored positively before the drug. Clinical grade assigned by method of Isbell et al.

A-379

TABLE 2.

Effect of 1.0 Mg./Kg. of Phenoxybenzamine on Response to 0.4 - 0.6 Mg./70 Kg. of Epinephrine.

EASURE	BEFORE PHENOXYBENZAMINE		AFTER PHENOXYBENZAMINE	
	Placebo	Epinephrine	Epinephrine	Placebo
ulse Rate	- 331 ± 94	+ 433 ± 186	+ 486 ± 95	- 318 ± 46
ystolic Blood ressure	- 187 ± 242	+ 453 ± 197	+ 285 ± 182	- 173 ± 97
iastolic Blood ressure	+ 142 ± 306	- 441 ± 219	- 657 ± 340	+ 208 ± 71

Figures are means ± standard errors of observations on 4 subjects. They represent time-action calculations (areas) expressed as beat-minutes (pulse), and mm. minutes (blood pressure). A positive figure indicates an increase over predrug measurements; a negative figure, a decrease.

TABLE 3.

Effect of 2.5 Mg./Kg. (Three Divided Doses) of Phenoxybenzamine on Response to 0.6 Mg. Epinephrine /70 Kg.

E[illegible]URE	BEFORE PHENOXYBENZAMINE		AFTER PHENOXYBENZAMINE	
	Placebo	Epinephrine	(1) Epinephrine	(2) Epinephrine
ulse Rate	- 273 ± 57	+ 545 ± 122	+ 780 ± 144	+ 684 ± 99
ystolic Blood ressure	- 129 ± 127	+ 459 ± 126	+ 299 ± 129	+ 90 ± 162
iastolic Blood ressure	+ 84 ± 74	- 552 ± 91	-1022 ± 148	-1286 ± 442

(1) Tested two hours after last dose of phenoxybenzamine.

(2) Tested five hours after last dose of phenoxybenzamine.

Figures are means ± standard errors of observations on 8 subjects.

4-377

TABLE 4.

Effect of 2.5 Mg./Kg. (Three Divided Doses) of Phenoxybenzamine on the Reaction Induced by 1.0 Mg./Kg. of LSD.

EASURE	TREATMENT			
	LSD Placebo Plus Phenoxybenzamine Placebo	LSD Plus Phenoxybenzamine Placebo	LSD Plus Phenoxybenzamine	LSD Placebo Plus Phenoxybenzamine
ulse Rate, ecumbent	+ 20.8 ± 5.2	+ 56 ± 18.7	+ 77.4 ± 13.0	+ 48.0 ± 10.1
ulse Rate, tanding	+ 36.3 ± 18.5	+ 12 ± 23.2	+ 16.0 ± 39.8	+ 157 ± 45
ystolic Blood ressure, Recumbent	+ 27.0 ± 25.4	+ 69.9 ± 9.3	+ 75.2 ± 10.9	+ 38.4 ± 12.8
upillary Size	+ 3.15 ± 1.3	+ 14.2 ± 1.5	+ 9.5 ± 0.7	- 1.4 ± 3.5
tellar Reflex	- 5.0 ± 1.7	+ 6.65 ± 1.2	+ 8.35 ± 1.6	+ 0.9 ± 1.12
er of Answers	0.2 ± 0.08	33 ± 12	47 ± 15	0.1 ± 0.9
cal Grade	0 ± 0	1.65 ± 0.37	1.85 ± 0.37	0 ± 0

Figures are means ± standard errors of observations on 10 subjects.